Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Hepatitis B Virus (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations

- All pregnant women should be tested for hepatitis B surface antigen (HBsAg) during an early prenatal visit **(AI)**. Testing should be repeated in late pregnancy for HBsAg-negative women at high risk of hepatitis B virus (HBV) infection (e.g., injection-drug users, women with intercurrent sexually transmitted diseases, women with multiple sex partners) **(BIII)**.
- All infants born to HBsAg-positive women, including HIV-co-infected women, should receive hepatitis B vaccine and hepatitis B immune globulin within 12 hours after birth, a second dose of hepatitis B vaccine at age 1 to 2 months, and a third dose at age 6 months **(AI)**.
- HIV-infected infants, children, and adolescents should be tested for HBsAg as soon as possible after HIV diagnosis **(AII)**.
- HIV-infected infants, children, and adolescents should be tested for quantitative anti-HBs and HBsAg 1 to 2 months after completing the vaccination series. If anti-HBs levels are <10 mIU/mL and the HBsAg result is negative, they should be revaccinated with a second, 3-dose series of HBV vaccine followed in 1 to 2 months by repeat testing for anti-HBs **(AIII)**.
- Antiviral therapy is not warranted in children without necroinflammatory liver disease **(BIII)**. Treatment is not recommended for children with immunotolerant chronic HBV infection (i.e, HBeAg positive, normal serum transaminase levels despite detectable HBV DNA) or inactive carriers (i.e. HBeAg negative, normal serum transaminase levels despite detectable HBV DNA) **(BII)**.
- Indications for treatment of chronic HBV infection in HIV-co-infected children are the same as in HBV-infected and HIV-uninfected children:
  - Evidence of ongoing HBV viral replication, as indicated by serum HBV DNA (>10,000–100,000 international units/ml for >6 months) and persistent elevation of serum transaminase levels (at least twice the upper limit of normal for >6 months), or
  - Evidence of chronic hepatitis on liver biopsy **(BII)**.
- Standard interferon-alfa (IFN-α), IFN-2a or IFN-2b, is recommended for treating chronic HBV infection with compensated liver disease in HIV-uninfected children aged ≥2 years to <12 years who warrant treatment **(AI)**. IFN-α therapy or oral antiviral therapy with adefovir or tenofovir is recommended for treating chronic HBV infection with compensated liver disease in HIV-uninfected children aged ≥12 years **(AI)**. IFN-α therapy in combination with oral antiviral therapy cannot be recommended for pediatric HBV infection in HIV-uninfected children until more data are available **(BII)**.
- In HIV/HBV coinfected children who do not require combination antiretroviral therapy (cART) for their HIV infection, IFN-α therapy is the preferred agent to treat chronic hepatitis B **(BIII)**, whereas adefovir can be considered in children age 12 years or older **(BIII)**.
- Treatment options for HIV/HBV co-infected children who meet criteria for HBV therapy and who are already receiving lamivudine- or emtricitabine-containing, HIV-suppressive cART include standard IFN- α therapy **(BIII)**, or adefovir if the child can receive adult dosing **(BIII)**, or use of tenofovir disoproxil fumarate (tenofovir) (with continued lamivudine or emtricitabine) in the cART regimen in children aged ≥2 years **(BIII)**.
- HIV/HBV-coinfected children should not be given lamivudine or emtricitabine for treatment of chronic HBV unless accompanied by additional anti-HIV drugs in a cART regimen **(CIII)**.
- For HIV/HBV-coinfected children who require treatment of both infections, a cART regimen that includes lamivudine (or emtricitabine) is recommended **(BIII)**.
- For HIV/HBV-coinfected children aged ≥ 2 years who require treatment for HIV but not HBV infection or treatment for both infections, a cART regimen that includes tenofovir and an anti-HBV nucleoside (either lamivudine or emtricitabine) can be considered **(BIII)**.
- The dose of lamivudine required to treat HIV infection is higher than that used to treat pediatric chronic hepatitis B infection; therefore, the higher dose of lamivudine should be used in HIV/HBV-coinfected children to avoid development of lamivudine-resistant HIV **(AIII)**.
- Lamivudine and emtricitabine should be considered interchangeable for treatment of chronic hepatitis B and not additive **(BIII)**.
- For hepatitis B e antigen (HBeAg)-positive patients who are HIV-uninfected, treatment with anti-HBV drugs should be continued until HBeAg seroconversion has been achieved and >6 months of additional treatment has been completed after the appearance of anti-HBeAg **(BI*)**. However, treatment with lamivudine or other anti-HBV drugs with anti-HIV activity should be continued indefinitely in children with HIV/HBV co-infection, even if HBeAg seroconversion occurs **(CIII)**.
- If discontinuation of therapy for chronic HBV results in hepatic flare, therapy for chronic HBV infection should be reinstituted **(BIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Chronic hepatitis B virus (HBV) infection is defined as persistence of serum hepatitis B surface antigen (HBsAg) for >6 months. The risk of developing chronic HBV infection after acute infection correlates inversely with age and immune competence at HBV infection. In HBV-infected patients, chronic HBV infection develops in about 90% of infants, 25% to 50% of children aged 1 to 5 years, and 6% to 10% of older children and adolescents; individuals with immunocompromising conditions (e.g., renal failure) are also at increased risk of developing chronic HBV infection.[1-4]

Infant and childhood HBV infection can be acquired perinatally, parenterally, or postnatally through household contact. It can also be acquired parentally or through sexual transmission. HIV/HBV-coinfected pregnant women can transmit HIV, HBV, or both to their infants; it is not known if maternal HIV coinfection modifies the risk of HBV perinatal transmission. Horizontal transmission of HBV can occur through interpersonal contact with non-intact skin or mucous membranes with blood or body fluids that contain HBV (e.g., injuries, wounds) or from sharing household objects (e.g., toothbrushes, razors). Universal hepatitis B vaccination of newborns has dramatically lowered chronic HBV infection in children and reduced the rates of HBV-related morbidity and mortality in the United States. The risk from blood transfusions in countries with blood bank screening is estimated to be very low (1.37 per million donations).[5] Maternal HBV infection is not a contraindication to breastfeeding.

Adolescents are at risk of HBV infection through sexual activity or injection-drug use. In a study of HIV-infected adolescents infected through sexual activity or injection-drug use at 43 Pediatric AIDS Clinical Trial Group centers, 19% had evidence of current or resolved HBV infection; the rate of current or resolved HBV infection in HIV-infected adolescent girls was twice the U.S. population-based rates for HIV-uninfected adolescent girls and, for adolescent boys, nearly seven times higher.[6] Substance abuse and sexual activity increase the risk of HIV/HBV coinfection in adolescents, particularly in men who have sex with men (MSM).[7]

Most children who acquire HBV perinatally are initially immunotolerant to HBV and may remain immunotolerant for a decade or more. Although these children have high HBV DNA levels, serum transaminase levels are usually normal, and necroinflammatory liver disease is minimal. Childhood-acquired HBV infection, in contrast, is characterized by lower HBV DNA levels, greater serum transaminase elevation, and higher necroinflammatory liver disease than in perinatally acquired HBV infection.[8]

Data from the National Health and Nutrition Examination Survey, 1999–2004, indicate that 0.51% (95% CI: 0.3%–0.9%) of children aged 6 to 19 years had ever been infected with HBV.[9] Only 1 small case series exists on the prevalence of chronic HBV infection in HIV-infected children at an inner city hospital in the United States, finding 2.6% prevalence in 228 HIV-infected children.[10]

Clinical Manifestations

Most acute HBV infections in children are asymptomatic.[11] Prodromal symptoms of lethargy, malaise, fatigue, nausea, and anorexia can occur. Jaundice and right-upper-quadrant pain can follow and, less commonly, hepatomegaly and splenomegaly. Gianotti-Crosti syndrome (papular acrodermatitis), urticaria, macular rash, or purpuric lesions may be seen in acute HBV infection. Extrahepatic manifestations associated with circulating immune complexes that have been reported in HBV-infected children include arthralgias, arthritis, polyarteritis nodosa, thrombocytopenia, and glomerulonephritis. However, rare cases of acute hepatic failure have occurred during perinatal and childhood HBV infection.[12,13]

Most children with chronic HBV infection are asymptomatic. One quarter of infants and children with chronic HBV eventually will develop cirrhosis or hepatocellular carcinoma (HCC).[14,15] However, these sequelae usually develop over 2 to 3 decades and rarely occur during childhood.[16,17] Development of HCC correlates with HBV DNA levels and duration of HBV infection, with the highest risk in people infected in early life.[18] HIV/HBV-coinfected adults are at increased risk of cirrhosis, end-stage liver disease, and liver-related mortality.[19]

Diagnosis

Testing for HBV infection should be performed in any child whose mother is known to be infected with HBV as well as children from groups at high risk of HBV infection, including those who are HIV-infected and who are foreign-born in regions of high and intermediate HBV endemicity (HBsAg-positive prevalence ≥2%). Adolescents and young adults with HIV infection, histories of injection-drug use, high-risk sexual contact, or MSM, should also undergo testing for HBV infection. Based on high prevalence of HBV infection in HIV-infected children and adolescents, HIV-infected children and adolescents and HIV-uninfected infants born to HBsAg-positive women should be tested for HBsAg as soon as possible after HIV diagnosis **(AII)**.[6,7,20]

HBsAg is the first marker detectable in serum, appearing 30 days after infection; it precedes the elevation of serum aminotransferase levels and the onset of symptoms. Necroinflammatory liver disease then can occur, during which serum transaminase levels increase, along with high HBV DNA levels and HBeAg positivity. HBeAg correlates with viral replication, DNA polymerase activity, infectivity, and increased severity of liver disease. Antibody to hepatitis B core antigen (anti-hepatitis B core antigen [HBc] immunoglobulin M [IgM]) appears 2 weeks after HBsAg and the anti-HBc immunoglobulin G (IgG) persists for life, but should not be confused with passively transferred maternal anti-HBc IgG that can be detectable in the infant up to ages 12 to 18 months or later. In self-limited infections, HBsAg is usually eliminated in 1 to 2 months, and hepatitis B surface antibody (anti-HBs) develops during convalescence. Anti-HBs indicates immunity from HBV infection. Despite immunity, HBV is incorporated into the human genome, where it can reactivate years later if a person becomes immunocompromised.[21] After recovery from natural infection, both anti-HBs and anti-HBc usually are present. In patients who become chronically infected (i.e., persistently positive for HBsAg beyond 6 months), anti-HBs is undetectable. Patients who have been vaccinated may have detectable anti-HBs but not anti-HBc or HBsAg. Patients who may have been inadvertently vaccinated after recovery from HBV infection should have detectable anti-HBs and anti-HBc upon post-vaccination testing (see Table 1, located at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5416a1.htm#tab1, for review of interpretation of serologic test results for HBV infection).

HBeAg seroconversion, defined as loss of HBeAg, followed by the production of antibodies to HBeAg (e.g., anti-HBe), usually heralds transition of the HBV-infected person to the inactive carrier state (HBsAg remains positive); however, some patients may develop HBeAg-negative chronic hepatitis. Variable rates of HBeAg seroconversion have been reported in children infected perinatally with HBV ranging from 10% to 75% in the first 2 to 4 decades but it is very infrequent in children aged <3 years.[22,23] In contrast, higher rates of HBeAg seroconversion occur in childhood-acquired HBV infection, with 70% to 80% of children acquiring anti-HBe by the second decade of life.[16] HBeAg seroconversion usually is followed by reduction in serum HBV DNA levels, an initial increase and then subsequent normalization of serum transaminase levels, followed by resolution of necroinflammatory liver disease.[16] Development of cirrhosis and HCC is more common in patients with delayed HBeAg seroconversion.[24] HBeAg-negative infection (pre-core mutant) is uncommon in children.[3]

HBV DNA is a marker for HBV replication. In the active phase of chronic hepatitis B, high HBV DNA levels have been associated with necroinflammatory liver disease. Children infected perinatally, however, may remain in an immunotolerant phase with high levels of HBV DNA without evidence of liver damage and normal serum aminotransferase levels. Quantitative DNA assays may help determine the need for treatment and for evaluating treatment response. Although not necessary for diagnostic purposes, liver biopsy may be useful to assess the degree of liver damage and determine the need for treatment.

Prevention Recommendations

Preventing Exposure

All pregnant women should be tested for HBsAg during the first prenatal visit **(AI)**. Testing should be repeated in late pregnancy for HBsAg-negative women at high risk of HBV infection (e.g., injection-drug users, women with intercurrent sexually transmitted diseases, women with multiple sex partners) **(BIII)**.

Pregnancy is not a contraindication or precaution to hepatitis B vaccination for women who have not previously been vaccinated; current hepatitis B vaccines contain noninfectious HBsAg and should cause no risk to the fetus. Pregnant women who are identified as being at risk of HBV infection during pregnancy should be vaccinated.[25]

Preventing Disease

All infants born to HBV-infected women, including HIV co-infected women, should receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth, a second dose of hepatitis B vaccine at age 1 to 2 months, and a third dose at age 6 months, but not before age 24 weeks **(AI)** (Figures 1 and 2).[26] For preterm infants weighing <2000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of hepatitis B vaccine in these infants; 3 additional doses of vaccine (for a total of 4 doses) should be administered beginning when the infant reaches 1 month of age **(AI)**.[26] In addition, term and preterm (birth weight <2000 g) infants born to women whose HBsAg status is unknown at delivery should receive the first dose of hepatitis B vaccine within 12 hours of birth. Infants weighing <2000 g should also receive HBIG within 12 hours of birth. Women with unknown HBsAg status should be tested as soon as possible. HBIG should be administered to term infants born to women whose HBsAg-test is found to be positive, or within 7 days of life when a mother's test results remain unknown.[26]

A 3-dose hepatitis B vaccine regimen is 70% to 95% effective in preventing HBV infection in HBV-exposed infants and combined with HBIG, is 85% to 95% effective. Postvaccination testing for anti-HBs and HBsAg should be performed at age 9 to 18 months in infants born to HBsAg-positive women **(BIII)**. The level of anti-HBs that is considered protective is ≥10 mIU/mL. Infants who are HBsAg-negative and have anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series of hepatitis B vaccine and retested 1 to 2 months after the final vaccine dose **(BIII)**.[26]

The 3-dose series of hepatitis B vaccine also is recommended for *all* children and adolescents aged <19 years who were not previously vaccinated. However, antibody responses to hepatitis B vaccination may be diminished in HIV-infected children, especially in older children or those with CD4 T lymphocyte (CD4 cell) counts <200 cells/mm^3.[27,28]

For this reason, HIV-infected infants, children, and adolescents should be tested for quantitative anti-HBs 1 to 2 months after completing the vaccination series and, if anti-HBs levels are <10 mIU/mL, revaccinated with a second 3-dose series of hepatitis B vaccine **(AIII)**.

Limited data suggest modified hepatitis B vaccine dosing regimens, including a doubling of the standard antigen dose and use of combined hepatitis A and B (HAV/HBV) vaccine, can increase response rates in HIV-uninfected non-responders[29] and in HIV-infected adults and adolescents.[30-32] Therefore, use of double-dose HBV vaccine or combination HAV/HBV vaccine may be considered for HBV vaccination in HIV-infected adolescents **(BI)**.

Waning of HBsAb levels below 10 mIU/mL after HBV re-immunization in HIV-infected children is common, but the need for booster doses of hepatitis B vaccine in HIV-infected individuals has not been determined.[33] The American Academy of Pediatrics Committee on Infectious Disease recommends annual anti-HBs testing and booster doses when the anti-HBs levels decline to <10 mIU/mL for hemodialysis patients and other immunocompromised people at continued risk of hepatitis B infection **(CIII)**.[34] HBV-infected children should be advised not to share toothbrushes or other personal-care articles that might be contaminated with blood (e.g., razors, tweezers, nail clippers) and to cover open or draining wounds. Although efficiency of sexual transmission of HBV is relatively low, safe-sex practices should be encouraged for all sexually active HIV-infected adolescents and young adults; barrier precautions (e.g., latex condoms) are recommended to reduce the risk of exposure to sexually transmitted pathogens, including HBV.

Treatment Recommendations

Treating Disease

General Issues

All children should receive HAV vaccination at age 12 to 23 months with the 2 doses in the series administered at least 6 months apart.[35] Children who are not fully vaccinated by age 2 years can be vaccinated at subsequent visits. The hepatitis A vaccine is also recommended for children aged ≥24 months who were not previously vaccinated and who have chronic liver disease (including chronic HBV infection) and other chronic diseases (Figures 1 and 2).

Treatment of pediatric HBV infection should be based on multiple factors, including a child's age, age at acquisition of infection, HBV DNA levels, and serum transaminase levels. Antiviral therapy regimens for chronic HBV are approved only for children aged >2 years who have compensated liver disease.

HIV-infected children who are not receiving anti-HBV therapy should be closely monitored with determination of serum aminotransferase levels every 6 months. If serum transaminase levels are persistently elevated (more than twofold the upper limit of normal for ≥6 months), HBeAg, anti-HBe, and HBV DNA levels should be obtained before the initiation of anti-HBV therapy. Assessment of serum transaminases and HBV DNA levels over time can identify patients who may be in the process of spontaneous HBeAg seroconversion and who would thus not require treatment. Liver biopsy is not required before treatment but may help to determine the severity of hepatic inflammation and fibrosis and to exclude other causes of liver disease.[36,37]

No clear recommendations exist for treating chronic childhood HBV infection. HBV-infected children often have milder disease than adults and may show spontaneous HBeAg seroconversion. Few large randomized controlled trials exist of antiviral therapies for chronic HBV infection in childhood. Moreover, the long-term safety of many of the agents used to treat chronic HBV infection in adults is unknown in children. However, pediatric liver experts at a 2010 consensus meeting recommended that anti-HBV treatment be considered in children aged >2 years with chronic HBV infection and a duration of necroinflammatory liver disease >6 months.[36]

Indications for treatment of chronic HBV infection in HIV-coinfected children are the same as in HBV-infected, HIV-uninfected children:

- Evidence of ongoing HBV viral replication, as indicated by serum HBV DNA (>10,000–100,000 IU/mL), irrespective of HBeAg positivity, for >6 months and persistent elevation of serum transaminase levels (at least twice the upper limit of normal for >6 months), or
- Evidence of chronic hepatitis on liver biopsy **(BII)**.[3,38]

Children without necroinflammatory liver disease do not warrant anti-HBV therapy **(BIII)**. Anti-HBV treatment is not recommended for children with immunotolerant chronic HBV infection (i.e., HBeAg positive, normal serum transaminase levels despite detectable HBV DNA) or inactive carriers (i.e. HBeAg negative, normal serum transaminase levels despite detectable HBV DNA) **(BII)**.

The goals of treatment for children with chronic HBV infection are identical to those for adults: suppression of HBV replication, normalization of serum transaminase levels, acceleration of HBeAg seroconversion (in those who are HBeAg positive), preservation of liver architecture, and prevention of long-term sequelae, such as cirrhosis and HCC.

Treatment of chronic HBV infection is evolving; consultation with providers with expertise in treating chronic HBV infection in children is recommended.

Treating Chronic Hepatitis B Infection in Adults and Adolescents

Seven medications have been approved to treat chronic HBV infection in adults: interferons (both standard and pegylated), nucleoside analogues (i.e., lamivudine, telbivudine, and entecavir), and the nucleotide analogues,

adefovir and tenofovir disoproxil fumarate (tenofovir). The FDA-approved HIV antiretroviral (ARV) medication emtricitabine also has significant activity against HBV, although it is not approved for this indication. Preferred initial therapies for adults who have chronic HBV without HIV infection include pegylated interferon-alfa (PEG-IFN-α), entecavir, or adefovir monotherapy. In HIV-infected adults who have chronic HBV infection, treatment for hepatitis B should be considered for those who are HBeAg-positive with HBV DNA ≥20,000 IU/mL (>10^5 copies/mL), HBeAg-negative with HBV DNA ≥2000 IU/mL (>10^4 copies/mL), patients who have persistent serum transaminase elevation, and those with evidence of cirrhosis or fibrosis.[19] Treatment of HBV infection is now recommended for all adults with concomitant HIV infection (*Adult Opportunistic Infection* and *Antiretroviral Guidelines*). This has not been recommended for children, however, and given the lack of data on this issue, a similar recommendation cannot be made at this point.

Treatment options for HBV in HIV-infected patients must account for the goals of therapy and the impact treatment may have on both HIV and HBV replication. In coinfected patients who require treatment for chronic HBV, HIV, or both, many experts would initiate a fully suppressive combined antiretroviral therapy (cART) regimen that includes two drugs active against HBV (tenofovir and either lamivudine or emtricitabine). This approach may reduce the risk of immune reconstitution inflammatory syndrome (IRIS), particularly in patients with advanced immunodeficiency. The combination of tenofovir with lamivudine was demonstrated to be more effective in suppressing HBV in coinfected adults than either drug alone and prevents development of lamivudine resistance.[39] In instances in which HIV treatment cannot be given but treatment of HBV infection is needed, PEG-IFN-α can be used alone because it does not lead to development of drug-resistant HIV or HBV mutants. Anti-HBV drugs with anti-HIV activity should not be given in the absence of a fully suppressive ARV regimen, because anti-HBV drugs such as tenofovir, entecavir, emtricitabine, lamivudine, and likely telbivudine given without additional ARV drugs in an HIV-suppressive regimen likely would produce resistant HIV in the recipient (see *Guidelines for Prevention and Treatment of Opportunistic Infection in Adolescents and Adults with HIV Infection*).

Treating Chronic Hepatitis B Infection in HIV-Uninfected Children

Only two drugs (IFN-α [standard] monotherapy or lamivudine monotherapy) are FDA-approved to treat chronic HBV in young children (1-11 years old) **(AI)**.[40,41] Four other drugs are approved for treatment of chronic HBV in older children: adefovir and tenofovir (children aged ≥12 years) and entecavir and telbivudine (children aged ≥16 years) **(AI)**.[42-45] While tenofovir is approved for treatment of HIV infection in children aged ≥2 years, it is not approved for treatment of HBV in children under 12 years old.

The limited pediatric trials of these agents show that although they are well-tolerated by children, response rates are similar to adults (~25% HBeAg seroconversion), and treatment generally does not eliminate HBV infection.[46,47] There is some evidence for enhanced loss of HBsAg in children treated with IFN in comparison to those treated with lamivudine.[40,48] In HIV-uninfected children, HBeAg seroconversion rates after 1 year of treatment are similar.[3] IFN-α treatment is administered for only 6 months but requires subcutaneous administration and has more frequent side effects, including growth impairment. Although lamivudine is administered orally and has a lower rate of side effects, it requires a longer duration of therapy and has a high rate of resistance if taken for an extended time.[3]

Although various combination regimens involving sequential or concurrent lamivudine and standard or PEG-IFN-α have been studied in children or adults with chronic HBV, superior treatment response with combination therapy over monotherapy with standard or PEG-IFN-α or lamivudine has not been demonstrated; however, lamivudine resistance rates may be lower with combination therapy.[49-58] A recent study of children with immunotolerant HBV infection suggested possible benefit from sequential lamivudine and IFN-α therapy, with 78% of patients clearing HBV DNA by the end of treatment.[57]

However, IFN-α (standard or pegylated) therapy in combination with oral antiviral therapy cannot be recommended for HBV infection in HIV-uninfected children until more data are available **(BII)**.

Treating HBV/HIV-Coinfected Children

None of the clinical studies of treatment of chronic HBV infection have specifically studied children with HIV/HBV coinfection. Choice of antiviral therapy for the HIV/HBV coinfected child involves consideration of whether HBV treatment, HIV treatment or treatment for both infections is warranted. Further study is needed to inform recommendations for antiviral therapy of children and adolecents with HIV/HBV coinfection.

If treatment of chronic HBV but not HIV infection is indicated, standard IFN-α is the preferred agent **(BIII)**. Adefovir also can be considered in children aged 12 years or older **(BIII)**. Antiviral drugs with activity against HIV (e.g., lamivudine, emtricitabine, tenofovir, entecavir, and likely telbivudine) should be avoided in the absence of a fully suppressive cART regimen to prevent development of drug-resistant HIV mutations. Despite *in vitro* evidence of anti-HIV activity of adefovir, there is no clinical evidence that adefovir monotherapy induces HIV drug resistance.[59]

If treatment of HIV infection but not chronic HBV is indicated, avoiding use of a cART regimen that contains only one ARV drug with activity against HBV (e.g., lamivudine, emtricitabine, or tenofovir) can prevent development of HBV drug resistance. Thus, in coinfected children who can receive tenofovir, use of a cART regimen that contains two drugs effective against HBV (tenofovir plus lamivudine or emtricitabine) can be considered **(BIII)**. However, for coinfected children aged < 2 years who need HIV but not HBV treatment, many experts would use a standard cART regimen that includes lamivudine (or emtricitabine). The optimal treatment approach needs further study.

If treatment for both HIV and chronic HBV is indicated and the child is lamivudine-naive, a cART regimen that includes lamivudine (or emtricitabine) is recommended **(BIII)**. A regimen containing tenofovir and lamivudine (or emtricitabine) should be considered for use in HIV-infected children aged ≥2 years, based on extrapolation from evidence in adults with HIV/HBV coinfection and adolescents with HBV monoinfection[42] but limited by absence of data evaluating use of tenofovir for treatment of HBV infection in HBV-monoinfected or HIV/HBV-coinfected children or HIV/HBV-coinfected adolescents **(BIII)**.

If treatment for HIV and chronic HBV is indicated, a child is already receiving HIV-suppressive cART including lamivudine (or emtricitabine), and plasma HBV DNA is detectable, HBV lamivudine resistance can be assumed. However, because HBV drug-resistant isolates may have lower replicative capacity, some experts recommend no change in therapy, although this recommendation is controversial **(CIII)**. Treatment options for such children who require HBV therapy include adding standard IFN-α **(BIII)**, or adefovir in children who can receive adult dosing **(BIII)**, or use of tenofovir (with continued lamivudine or emtricitabine) in the cART regimen in children aged ≥2 years **(BIII)**.

Data are insufficient on other anti-HBV drugs in children to make recommendations.

Interferons

Standard IFN-α-2a or -2b has received the most study in children who have chronic HBV infection (without HIV infection) and is recommended for treating chronic HBV infection with compensated liver disease in HIV-uninfected children aged ≥2 years who warrant treatment **(AI)**.

In a review of 6 randomized clinical trials in 240 HBV-infected children aged >1.5 years, IFN-α therapy resulted in HBV DNA clearance in 35% of treated children, HBeAg clearance in 10%, and normalization of serum transaminase levels in 39% at treatment completion.[60] Six to 18 months after therapy discontinuation, 29% of children had persistent clearance of HBV DNA, and 23% demonstrated HBeAg clearance. Children most likely to respond to IFN treatment are younger and have higher baseline serum transaminase levels and lower baseline HBV DNA levels.[46,61-63] Response is less likely (10%) in those with normal serum transaminase levels, high HBV DNA levels, HBV genotypes C or D, or HBeAg-negative chronic HBV infection.

IFN-α therapy is the preferred agent to treat chronic hepatitis B in HIV-coinfected children who do not require cART for their HIV infection **(BIII)**.

The standard course of IFN-α therapy for HIV-uninfected children is 24 weeks. PEG-IFN-α, which results in

more sustained plasma interferon concentrations and can be administered by injection once weekly for 48 weeks, has proven superior to standard IFN-α in treating HBV-infected adults.[50,64] However, the limited data on use of pegylated IFN-α in children come from treatment of hepatitis C infection, and appropriate dosing information is not available for use of pegylated IFN-α to treat chronic HBV infection in children.[65-67]

Lamivudine

Lamivudine (3TC) is an oral nucleoside analogue that inhibits HBV replication. It is approved for use in children aged 2 to 17 years who have compensated liver disease from chronic HBV infection. In a placebo-controlled trial in HIV-uninfected children with chronic HBV infection, lamivudine was well tolerated, with virologic response (clearance of HBV DNA and HBeAg) in 23% of children receiving 52 weeks of lamivudine therapy, compared with 13% in placebo recipients.[41] Response rates were higher (35%) for children with baseline serum transaminases more than two times normal.[41] In a 2-year, open-label extension of this study, 213 children who remained HBeAg-positive after 1 year of therapy were continued on lamivudine treatment; virologic response was seen in 21% of the original lamivudine recipients, compared with 30% of prior placebo recipients, indicating that additional clinical response could occur over time with prolonged treatment.[68] However, longer duration of lamivudine therapy also was associated with progressive development of lamivudine-resistant HBV, with base pair substitutions at the tyrosine-methionine-aspartate-aspartate (YMDD) locus of HBV DNA polymerase.

Lamivudine should not be used as a single agent for treatment of chronic HBV infection in HIV-infected children who are not receiving cART because of the risk of HIV resistance to lamivudine **(CIII)**; as discussed above, lamivudine should be used only in HIV/HBV-coinfected children in combination with other ARV drugs in a cART regimen **(BIII)**. The dose of lamivudine required to treat HIV infection is higher than that for treating pediatric chronic HBV infection alone; therefore, the higher dose of lamivudine should be used in HIV/HBV-coinfected children to avoid development of lamivudine-resistant HIV **(AIII)**.

Lamivudine resistance should be suspected if HBV DNA levels increase by 1 to 2 log during antiviral therapy. Such increases may precede increases in serum transaminase levels (hepatic flare) and liver decompensation.[63]

Emtricitabine

Emtricitabine is structurally similar to lamivudine and is active against HBV and HIV, although not approved for treatment of chronic HBV infection. Like lamivudine, emtricitabine also is associated with relatively rapid onset of HBV and HIV drug resistance, and patients with suspected lamivudine resistance should be assumed to have cross-resistance to emtricitabine.

Lamivudine and emtricitabine should be considered interchangeable for treatment of chronic HBV infection and not additive **(AIII)**. As with lamivudine, emtricitabine should not be used to treat chronic HBV infection in coinfected children who are not being treated with cART for their HIV infection because of the risk of HIV-associated resistance mutations **(CIII)**.

Adefovir

Adefovir dipivoxil is an oral nucleotide analogue active against HBV. Although active against HBV, adefovir has minimal anti-HIV activity, and HIV resistance has not been observed in patients receiving a 10-mg daily dose of adefovir for 48 weeks.[59] HBV resistance is much lower to adefovir than to lamivudine, reportedly 2% after 2 years, 4% after 3 years, and 18% after 4 years of therapy in adults.[69] These adefovir-associated mutations in HBV *Pol* gene result in only a modest (threefold to eightfold) increase in the 50% inhibitory concentration and are partially cross-resistant with tenofovir. Adefovir is now FDA-approved for adults who require treatment for chronic HBV infection but do not yet require treatment for HIV. Adefovir has been studied in HIV/HBV-coinfected adults with lamivudine-resistant HBV infection, and HBV suppression was demonstrated.[59] Safety and effectiveness of adefovir for treating chronic HBV infection in children has been reported.[43] In a randomized, placebo-controlled trial, adefovir was more effective than placebo in children age ≥12 years at suppressing viral replication and normalizing transaminases.

Tenofovir Disoproxil Fumarate (Tenofovir)

Tenofovir is a nucleotide analog structurally similar to adefovir that reduces HBV DNA levels in adults with lamivudine-resistant and wild-type HBV infection. A study in HIV/HBV-coinfected adults receiving stable cART comparing treatment with tenofovir or adefovir found similar efficacy in suppression of HBV DNA with no difference in toxicity.[70] Another study of HIV/HBV-coinfected adults receiving tenofovir in addition to lamivudine as part of their ARV regimen found that HBV DNA became undetectable in 30% of HBeAg-positive and 82% of HBeAg-negative patients, most of whom had lamivudine-resistant HBV infection.[59] As noted earlier, tenofovir is not approved for treatment of HBV infection in children aged <12 years, but tenofovir is approved as part of cART for HIV beginning at age 2 years.

However, for HIV/HBV-coinfected children aged ≥2 years who require treatment of both infections, tenofovir in combination with an anti-HBV nucleoside (either lamivudine or emtricitabine) can be considered **(BIII)**; a combined formulation of emtricitabine and tenofovir (Truvada) is available for adults. As with lamivudine and emtricitabine, tenofovir should not be used to treat chronic HBV in HIV-coinfected patients who are not receiving cART for HIV because of the risk of HIV-associated resistance mutations **(CIII)**.

Entecavir

Entecavir is an oral nucleoside analogue that inhibits HBV DNA polymerase. When compared to lamivudine, entecavir therapy results in greater HBV viral suppression, increased normalization of serum transaminase levels, improved liver histology, and lower HBV resistance rates.[71] HBV viral suppression also has been demonstrated in HIV/HBV-coinfected adults. Entecavir treatment is approved for treatment of chronic HBV in adults and is preferred for lamivudine-resistant HBV infections. However, it recently was demonstrated to have suppressive activity against HIV.[72] Entecavir should not be used in HIV/HBV-coinfected patients who are not receiving cART for HIV. Entecavir is approved for use in children aged ≥16 years; no data are available on safety and efficacy of entecavir in younger children.

Telbivudine

Telbivudine is a thymidine nucleoside analogue that was approved to treat chronic HBV in adults. It is well tolerated, but like lamivudine, resistance emerges over time, and telbivudine is not active against lamivudine-resistant HBV. No data are available on telbivudine in HIV/HBV-coinfected adults. Telbivudine is approved for use in children aged ≥16 years; no data are available on safety and efficacy of entecavir in younger children.

Duration of Therapy

The optimal duration of therapy in HIV/HBV-coinfected children is not known. The duration of IFN-α treatment in HIV-uninfected children with chronic HBV infection is 6 months. At least 1 year of lamivudine therapy is recommended for HIV-uninfected children who have chronic HBV infection, with continuation of medication for ≥6 months after documented HBeAg seroconversion.[46] The duration of IFN therapy in HIV-infected children with HBV infection in whom treatment is indicated should be at least 6 months **(CIII)**. Among HBeAg-positive children who are HIV-uninfected, treatment of chronic HBV infection with antivirals should be continued until HBeAg seroconversion has been achieved and ≥6 months of additional treatment has been completed after the appearance of anti-HBe **(BI*)**.

However, because lamivudine (or emtricitabine) and tenofovir would be administered only to HIV/HBV-coinfected children who need HIV treatment and as part of a suppressive ARV regimen, treatment with lamivudine (or other anti-HBV drugs with anti-HIV activity) should be continued indefinitely in children with HIV/HBV coinfection, even if HBeAg seroconversion occurs **(CIII)**.

Monitoring and Adverse Events (Including IRIS)

The parameters for successful therapy for chronic HBV infection are not well defined, but markers of improvement include decreased hepatic necroinflammatory disease, normalization of serum transaminase levels, reduction of HBV DNA levels, and HBeAg seroconversion. In children starting treatment for chronic

HBV infection, serum transaminase levels should be measured frequently at the start of therapy and then every 3 to 6 months. In children who are also beginning cART, some experts would monitor transaminase levels more frequently during the first few months of therapy (e.g, monthly for 3 months) because of the risk of IRIS (see below). Monitoring of response to treatment for chronic HBV infection is based on testing for HBV DNA and HBeAg and anti-HBe antibody on the same schedule as transaminase evaluations (every 3–6 months).

Close monitoring for relapse is needed after withdrawal of therapy. In patients who are HBeAg-negative, treatment should be continued until HBsAg clearance has been achieved **(BII)**.

In HIV/HBV-coinfected patients starting cART, serum transaminase elevations (flares) can occur as part of IRIS or secondary to cART-associated hepatotoxicity. HBV-associated liver injury is thought to be immune-mediated, and restoration of immunocompetence with ARV treatment may reactivate liver inflammation and damage. Initiation of cART without anti-HBV therapy can lead to re-activation of HBV. This does not represent a failure of cART but rather a sign of immune reconstitution. IRIS manifests by an increase in serum transaminase levels as the CD4 cell count increases during the first 6 to 12 weeks of cART. Thus, serum transaminase levels should be monitored closely after introduction of cART. In such situations, cART should be continued and treatment for HBV infection initiated. The prognosis for most IRIS cases is favorable because a robust inflammatory response may predict an excellent response to cART in terms of immune reconstitution, and perhaps, improved survival. In patients experiencing hepatic flare, differentiating between IRIS and drug-induced liver toxicity may be difficult, and no reliable clinical or laboratory predictor exists to distinguish between the two. Close collaboration of the HIV specialist with a specialist in hepatic disease is recommended for such patients; a hepatologist should be consulted promptly if elevated aminotransferases levels are associated with clinical jaundice or other evidence of liver dysfunction (e.g., serum albumin).

Clinical and laboratory exacerbations of hepatitis and hepatic flare also can occur in coinfected children receiving cART if agents with anti-HBV activity are discontinued. Generally, once ARV drugs with anti-HBV activity are begun in coinfected children, they should be continued indefinitely unless contraindicated **(CIII)**. If discontinuation of therapy for chronic HBV infection results in hepatic flare, therapy for chronic HBV should be re-instituted **(BIII)**.

Some clinicians recommend monitoring HBV-infected children or adolescents for HCC with baseline screening and then annual or twice yearly determinations of serum alpha-fetoprotein (AFP) levels and abdominal ultrasonography; however, no data support the benefit of such surveillance.[3,38,46,47] Current recommendations in HBV-infected, HIV-uninfected adults support abdominal ultrasonography in men aged >40 years and women aged >50 years. The use of AFP monitoring is controversial.

Adverse effects of IFN-α use in children, although frequent, usually are not severe or permanent; however, approximately 5% of children require treatment discontinuation. The most common side effects include an influenza-like syndrome, cytopenias, and neuropsychiatric effects. Influenza-like symptoms comprising fever, chills, headache, myalgia, arthralgia, abdominal pain, nausea, and vomiting are seen in 80% of patients during the first month of treatment. These side effects decrease substantially during the first 4 months of therapy; premedication with acetaminophen or ibuprofen may reduce side effects. Subtle personality changes, which resolve when therapy is discontinued, have been reported in 42% of children.[40] Depression and suicidal ideation also have been reported in clinical trials of children treated with IFN-α.[73] Ophthalmologic complications have been reported in clinical trials of children with pegylated IFN.[74] Neutropenia, which resolves after discontinuation of therapy, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Abnormalities in thyroid function (hypothyroidism or hyperthyroidism) have been reported with IFN-α therapy.[75] Loss of appetite with transient weight loss and impaired height growth can occur but usually resolves after completion of therapy.[76] Less commonly observed side effects of IFN-α include epistaxis and transient mild alopecia. Antinuclear auto-antibodies have been detected in some children treated with IFN-α.

IFN-α therapy is contraindicated in children with decompensated liver disease; severe cytopenia; severe renal, cardiac, or neuropsychiatric disorders; and autoimmune disease **(CIII)**.[77]

Elevation of serum transaminase levels has been reported during IFN-α therapy in children and adults but usually is not an indication to stop therapy; these flares may herald impending HBeAg seroconversion.[46] Children receiving IFN-α therapy should be monitored with frequent complete blood count and liver function tests, and serum level of thyroid-stimulating hormone should be determined at baseline and periodically (e.g., at least every 3 months) for the duration of treatment.

Lamivudine usually is well-tolerated in children; rare cases of lactic acidosis and pancreatitis have been reported in HIV/HBV-coinfected adults. tenofovir and adefovir can cause renal tubular disease. Patients receiving either drug should have baseline urinalysis and periodic urinalysis, serum creatinine and phosphate monitoring. Administration of other nephrotoxic agents increases the risk of renal toxicity. Tenofovir can lead to reduced bone density.

Managing Treatment Failure

Treatment failure is defined as ongoing HBV replication, persistent serum transaminase elevations, and the failure of HBeAg seroconversion in HBeAg-positive patients at the completion of therapy (for IFN) and after an adequate trial of oral anti-HBV antivirals (generally at least 6–12 months). In individuals with HBeAg-negative hepatitis, treatment failure is defined as ongoing HBV replication (>10,000 IU) and persistent serum transaminase elevations. Flares of liver disease with increasing HBV DNA levels can be seen with the development of resistance to lamivudine or emtricitabine.

In some children who have received initial treatment for chronic HBV infection with standard-dose IFN-α monotherapy, use of higher-dose IFN-α for retreatment improves response.[58,78,79]

Lamivudine also has been used as secondary therapy for young (<12 years old) HIV-uninfected children who have not responded to standard IFN-α therapy **(BI)**;[80-82] in HIV-infected children, initiation of a lamivudine-containing or emtricitabine-containing cART regimen (that also contains tenofovir, if aged ≥2 years) can be considered **(CIII)**.

For HIV/HBV coinfected children who develop lamivudine resistance during therapy, treatment options are more limited because of lack of data on use of adefovir, entecavir, and tenofovir for treatment of HBV infection in young children. Because these HBV drug-resistant isolates may have lower replicative capacity than wild-type HBV, some experts recommend continuing lamivudine or emtricitabine therapy in such cases **(CIII)**.

Alternatively, adding IFN-α can be considered or, in children old enough to receive adult doses of adefovir, adding that drug to the regimen can be considered **(CIII)**.

Preventing Recurrence

Not applicable.

Discontinuing Secondary Prophylaxis

Not applicable.

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Dosing Recommendations for Prevention and Treatment of HBV in HIV/HBV Coinfected Children

(page 1 of 2)

Preventive Regimen			
Indication	**First Choice**	**Alternative**	**Comments/Special Issues**
Primary Prophylaxis	• Hepatitis B vaccine • Combination of hepatitis B immunoglobulin and hepatitis B vaccine for infants born to mothers with hepatitis B infection	Hepatitis B immunoglobulin following exposure	See Figures 1 and 2 for detailed vaccine recommendations. Primary Prophylaxis Indicated for: • All individuals who are not HBV infected Criteria for Discontinuing Primary Prophylaxis: • N/A Criteria for Restarting Primary Prophylaxis: • N/A
Secondary Prophylaxis	Hepatitis A Vaccine	N/A	Secondary Prophylaxis Indicated for: • Chronically HBV-infected individuals to prevent further liver injury Criteria for Discontinuing Secondary Prophylaxis: • N/A Criteria for Restarting Secondary Prophylaxis: • N/A
Treatment	Treatment of Only HBV Required (Child Does Not Require cART): • IFN-α 3 million units/m^2 body surface area SQ 3 times a week for 1 week, followed by dose escalation to 6 million units/m^2 body surface area (max 10 million units/dose), to complete a 24-week course, or • For children aged ≥12 years, adefovir 10 mg by mouth once daily for a minimum of 12 months (uncertain if risk of HIV resistance) Treatment of Both HIV And HBV Required (Child Not Already Receiving 3TC or FTC) • 3TC 4 mg/kg body weight (maximum 150 mg) per dose by mouth twice daily as part of a fully suppressive cART regimen	• IFN-α 10 million units/m^2 body surface area SQ 3 times a week for 6 months (sometimes used for retreatment of failed lower-dose interferon therapy) • Alternative for 3TC: FTC 6 mg/kg body weight (maximum 200 mg) once daily	Indications for Treatment Include: • Detectable serum HBV DNA, irrespective of HBeAg status, for >6 months; and • Persistent (>6 months) elevation of serum transaminases (≥ twice the upper limit of normal); or • Evidence of chronic hepatitis on liver biopsy IFN-α is contraindicated in children with decompensated liver disease; significant cytopenias, severe renal, neuropsychiatric, or cardiac disorders; and autoimmune disease. Choice of HBV treatment options for HIV/HBV-co-infected children depends upon whether concurrent HIV treatment is warranted. 3TC and FTC have similar activity (and have cross-resistance) and should not be given together. FTC is not FDA-approved for treatment of HBV. Tenofovir is approved for use in treatment of HIV

Dosing Recommendations for Prevention and Treatment of HBV in HIV/HBV Coinfected Children

Preventive Regimen			
Indication	**First Choice**	**Alternative**	**Comments/Special Issues**
Treatment	• For children aged ≥2 years, include tenofovir as part of cART regimen with 3TC or FTC. For children aged ≥12, tenofovir dose is 300 mg once daily. For children aged <12 year, and 8 mg/kg body weight per dose once daily (maximum dose 300 mg) Treatment of Both HIV and HBV Required (Child Already Receiving cART Containing 3TC or FTC, Suggesting 3TC/FTC Resistance): • For children aged ≥2 years, include tenofovir as part of cART regimen with 3TC or FTC. For children aged ≥12 years, tenofovir dose is 300 mg once daily. For children aged <12 years, 8 mg/kg body weight per dose once daily (maximum dose 300 mg) • For children aged ≥12 years, add adefovir 10 mg by mouth once daily or entecavir 0.5 mg by mouth once daily in addition to cART regimen. • For children aged <12 years, give 6-month course of IFN-α as above in addition to cART regimen.		infection in children aged ≥2 years but it is not approved for treatment of HBV infection in children aged <12 years. It should only be used for HBV in HIV/HBV-infected children as part of a cART regimen. Adefovir is approved for use in children aged ≥12 years. ETV is not approved for use in children younger than age 16 years, but is under study in HIV-uninfected children for treatment of chronic hepatitis B. Can be considered for older HIV-infected children who can receive adult dosage. It should only be used for HBV in HIV/HBV-infected children who also receive an HIV-suppressive cART regimen. IRIS may be manifested by dramatic increase in transaminases as CD4 cell counts rise within the first 6 to 12 weeks of cART. It may be difficult to distinguish between drug-induced hepatotoxicity and other causes of hepatitis and IRIS. In children receiving tenofovir and 3TC or FTC, clinical and laboratory exacerbations of hepatitis (flare) may occur if the drug is discontinued; thus, once anti-HIV/HBV therapy has begun, it should be continued unless contraindicated or until the child has been treated for >6 months after HBeAg seroconversion and can be closely monitored on discontinuation. If anti-HBV therapy is discontinued and a flare occurs, reinstitution of therapy is recommended because a flare can be life threatening. Telbivudine has been approved for use in people aged ≥16 years with HBV; there are no data on safety or efficacy in children aged <16 years; a pharmacokinetic study is under way in HIV-uninfected children.

Key to Acronyms: 3TC = lamivudine; cART = combined antiretroviral therapy; CD4 = CD4 T lymphocyte; FTC = emtricitabine; HBeAg = hepatitis B antigen; HBV = hepatitis B virus; IFN-α = interferon alfa; IRIS = immune reconstitution inflammatory syndrome; SQ = subcutaneous; tenofovir = tenofovir disoproxil fumarate